CREUTZFELDT-JAKOB DISEASE SURVEILLANCE

IN THE UNITED KINGDOM

FOURTH ANNUAL REPORT

AUGUST 1995

The National CJD Surveillance Unit
Western General Hospital
Crewe Road, Edinburgh, EH4 2XU

Department of Epidemiology and Population Sciences
London School of Hygiene and Tropical Medicine
Keppel Street, London, WC1E 7HT

CONTENTS

SECTION 1 CLINICAL SURVEILLANCE

INTRODUCTION

The national surveillance of Creutzfeldt-Jakob disease (CJD) was initiated in May 1990 in response to a recommendation in the Report of the Working Party on Bovine Spongiform Encephalopathy (The Southwood Committee) and is funded by the Department of Health and the Scottish Home and Health Department. The primary aim of the project is to monitor CJD in order to identify any change in the pattern of this disease that might be attributable to the emergence of Bovine Spongiform Encephalopathy (BSE). This report documents the findings from the CJD Surveillance Project up to 30 April 1995.

NUMBERS OF CASES

Between the start of the prospective study in May 1990 and 30 April 1995, 411 suspected cases have been notified to the Surveillance Unit. 214 of these cases have been classified as definite or probable CJD according to previously described criteria and these cases are included in further analysis. The total number of cases by diagnostic category and the sources of notification are listed in Table 1. Deaths from Creutzfeldt-Jakob disease by calendar year (1985-1995) are listed in Table 2.

STATISTICAL ANALYSIS

Age, Sex, Temporal and Geographical Distribution of CJD

The following analyses are based on 149 cases of CJD dying in England and Wales between 1970 and 1979, 122 cases dying in England and Wales between 1980 and 1984, 130 cases dying in Great Britain, Northern Ireland and the Channel Islands between 1985 and 1989, 220 cases dying in Great Britain, Northern Ireland and the Channel Islands between 1st January 1990 and 30 April 1995, and 7 cases surviving beyond that date. Cases of Gerstmann-Straussler-Scheinker syndrome have been excluded. For comparisons across time periods, iatrogenic and familial cases of CJD have been included, since for the earlier time periods the type of case was not identified in this way and thus they cannot be excluded for these periods. Iatrogenic and familial cases have been excluded from the analyses of dietary and occupational risk factors and from the analysis of space-time clustering.

TABLE 1

REFERRALS OF SUSPECT CASES TO THE CJD SURVEILLANCE UNIT

1 MAY 1990 - 30 APRIL 1995

411 SUSPECTED CASES REFERRED

REFERRED FROM	DEFINITE	PROBABLE	POSSIBLE	OTHER	GSS	UNCLASSIFIED
Neurologist	108	27	21	74	4	1
Pathologist	38	0	1	12	1	0
General Physician	14	1	3	11	0	0
Death Certificate	6	3	7	24	0	2
Psychiatrist	0	1	0	10	0	0
EEG Dept	7	2	2	9	0	0
Other	6	1	5	10	0	0
TOTAL	179	35	39	150	5	3

TABLE 2

DEATHS FROM CREUTZFELDT-JAKOB DISEASE

By Calendar Year (1985-1995)

Year	Sporadic	Iatrogenic	Familial	GSS	TOTAL
1985	26	1	1	0	28
1986	26	0	0	0	26
1987	23	0	0	1	24
1988	21	1	1	0	23
1989	28	1	1	0	30
1990	26	5	0	0	31
1991	32	1	3	0	36
1992	44	2	4	1	51
1993	35	4	2	1	42
1994	53	1	0	1	55
1995 (to 30 April)	7	1	0	0	8

England and Wales

Figure 1 shows the number of deaths from Creutzfeldt-Jakob disease (definite and probable cases) in England and Wales, by year, from 1st January 1970 to 30th April 1995. Over the first fifteen years of this period (before the advent of BSE), there was a substantial increase in the crude rate of mortality from CJD (0.27/million/year, 1970-74; 0.35/million/year, 1975-79; 0.50/million/year, 1980-84). This increase may simply represent improved case ascertainment over the period. In the period 1985 to 1989, during which cases were identified retrospectively after the occurrence of BSE, the crude mortality rate was 0.47/million/year, slightly lower than in the preceding period. Over the period 1st January 1990 to 31st December 1994, for most of which period cases were ascertained prospectively by surveillance, the crude mortality rate rose to 0.76/million/year. Of the 185 deaths in England and Wales during this latter period, 167 were classified as sporadic cases, 9 as familial, and 9 as iatrogenic. The mortality rate for sporadic CJD during this period was 0.69/million/year.

Scotland, Northern Ireland and the Channel Islands

Figure 2 shows deaths from Creutzfeldt-Jakob disease in Scotland, Northern Ireland and the Channel Islands during the period 1st January 1985 to 30th April 1995. A total of 41 deaths were identified in Scotland, 15 between 1985 and 1989 (crude mortality rate = 0.60/million/year) and 24 between 1990 and 1994 (crude mortality rate = 0.97/million/year). Of these latter 24, 3 were iatrogenic cases. Excluding them produces a crude mortality rate of 0.83/million/year. In Northern Ireland 6 deaths were identified (0.75/million/year), and in the Channel Islands 1 death.

Figures 3 to 6 show age- and sex-specific death rates from CJD for each of the 4 different time periods. In the periods 1970-79 and 1980-84 mortality rates were highest among those in their late fifties and in their sixties and declined in those aged over 70. In those age groups with the highest rates, rates tended to be higher in females than males (Figures 3 and 4). In the period 1985-89, peak rates appeared to persist over a wider age range with the decline in rates not occurring until the late seventies (Figure 5). Post 1989, there was a decline in mortality among those aged 70-75 and a rise in mortality in those aged over 75 (Figure 6). During both the latter periods mortality rates in males and females appeared similar. The age range for sporadic cases in 1994 was 44-89 years.

Crude mortality rates by county for the periods up to 1984 and after 1984 are shown in Figures 7 and 8 respectively. In the earlier period, 1970 to 1984, the highest rates (over 1/million/year) were observed in Dyfed and Oxfordshire (Figure 7). In the later period the rates in both these counties were lower (Figure 8). Between 1985 and 1994, seven counties in England and Wales had rates above 1/million/year (Cornwall, Dorset, Avon, Powys, Gwynedd, Northants and Cumbria). In Scotland high rates were observed in Central and Grampian.

Standardised mortality ratios (SMRs) for the standard regions are shown in Figure 9 (for the period 1970 to 1984) and in Figure 10 (for the period 1985 to 1994). The highest SMR in the earlier period was in the South-East (127.3). This fell to 98.9 (101.6 excluding Scotland) in the later period. A large change was also observed in the South West (a rise from 99.5 to 145.2). Scotland, included for the first time in the second period, had a relatively high SMR (126.8). When Scotland was excluded from the analysis there was no strong evidence that the geographical distribution of rates differed between the two periods ($p = 0.21$).

There was, however, strong evidence that the overall rate in England and Wales, taking account of the age and sex distribution of the population, varied between the different time periods (70-79, 80-84, 85-89, 90-94) ($p < 0.0001$). Adjusting for age, sex and standard region, mortality rates were about 2½ times higher in the period 1990-94 than in the period 1970-79. Excluding the period 1970-79, when it is believed that under-ascertainment of cases is likely to have occurred, there is still evidence that mortality rates differed between the different time periods ($p = 0.0001$). Compared to the period 1980-84, when ascertainment had been thought to be fairly complete, mortality was 8% lower in the period 1985-89 (95% c.i. 29% lower to 18% higher) but 47% higher in the period 1990-94 (95% c.i. 17% to 85% higher). When the oldest age group (75 years and above) was excluded, the differences between these time periods remained statistically significant ($p = 0.01$), although the increase in the period 1990-94 relative to the period 1980-84 was reduced to 31% (95% c.i. 2% to 67%). This finding is compatible with the hypothesis that part of the apparent increase in mortality rates in 1990-94 may have been due to improved case ascertainment in the oldest age group (75 years and above) but indicates that there has also been an increase in reported incidence in younger age groups.

After controlling age, time period and standard region, mortality rates in females over the whole 25 year period were only slightly higher than those in males

(rate ratio = 1.12; p = 0.16). (In the earlier series a statistically significant excess of females had been observed).

COMMENT

Since the start of the surveillance project in 1990, the total annual number of cases of CJD identified in the United Kingdom has risen from 31 in 1990 to 55 in 1994. Part of this increase is due to the occurrence of increased numbers of iatrogenic cases of CJD and improved identification of familial cases of CJD. It is of note that no familial cases of CJD were identified in 1994 and this is almost certainly due to delays in obtaining molecular biological data in the past 12 months. Recent analysis has suggested that 2 of the 53 cases currently classified as sporadic are in fact mutation related cases although confirmation is awaited. It is therefore likely that a number of cases currently classified as sporadic for the year 1994 will be re-classified as familial when genetic data becomes available.

On the other hand, death certificates for England and Wales had not been available for the years 1993 and 1994, with the possibility that a small number of additional cases of CJD for these years might subsequently be identified. In recent weeks, death certificates for England and Wales for the year 1993 have been made available with a total of 39 cases certified of whom 30 had already been identified from other sources. Of the 9 previously unidentified cases, 2 have been classified as probable and 2 have been classified as autopsy-proven not CJD. Further information on the remaining 5 cases is awaited. This indicates that only a very small number of cases are identified from death certificates alone and that when certificates for the year 1994 become available, only a small number of additional cases are likely to be identified.

The incidence of CJD in the United Kingdom in 1994 is 0.93 cases/million/year representing the highest incidence of CJD since the start of surveillance. Comparison of the number of deaths from sporadic CJD under the age of 75 and over the age of 75 (Figures 11 and 12) indicates that a major component of the increased incidence of CJD relates to the identification of increased numbers of cases of CJD in the elderly. This was noted in the previous annual report and may be due to improved ascertainment of CJD in the elderly population in the United Kingdom. There has however also been a small increase in deaths from sporadic CJD in younger age groups in the year 1994.

One possible explanation for the increased number of cases is improved identification of cases of CJD and it is relevant to compare the United Kingdom results with those from other countries as there may have been a general

improvement in case ascertainment related to increased awareness of CJD. Comparison of the incidence of CJD in a number of countries in Europe has been possible through a grant from the European Community for the co-ordination of CJD surveillance (for the years 1993-1995). Incidence figures for CJD are also available from a number of other countries, primarily from published sources. Comparative incidence figures for CJD round the world are summarised in Table 3.

TABLE 3 ANNUAL INCIDENCE OF CREUTZFELDT-JAKOB DISEASE

COUNTRY	PERIOD	INCIDENCE CASES/ MILLION	COUNTRY	PERIOD	INCIDENCE CASES/ MILLION
Chile	1955-1972	0.10	Japan	1975-1977	0.45
	1973-1977	0.31			
	1978-1983	0.69			
			Netherlands	1993-1994	0.92
Czechoslovakia	1972-1986	0.66			
			New Zealand	1980-1989	0.88
France	1968-1977	0.34			
	1978-1982	0.58	Switzerland	1988-1990	0.80
	1992-1994	0.81			
			United Kingdom	1964-1973	0.09
Germany	1979-1990	0.31		1970-1979	0.31
	1993-1994	0.68		1980-1984	0.47
				1985-1989	0.46
Israel	1963-1972	0.75		1990-1994	0.82
	1963-1987	0.91			
			USA	1973-1977	0.26
Italy	1958-1971	0.05		1986-1988	0.83
	1972-1985	0.11			
	1993-1994	0.61			

These data indicate that the incidence of CJD has increased in each surveillance period in all countries in which serial surveillance of CJD has been carried out. It is also clear that the incidence figure of 0.93 cases/million/year for 1994 in the United Kingdom is comparable to the incidence of CJD in a number of countries within Europe and elsewhere.

In conclusion, there has been an increase in the incidence of CJD in the United Kingdom with a high figure of 0.93 for the year 1994. It would however be

premature to conclude that this indicates any additional risk factor for CJD in the United Kingdom as the incidence in other countries without BSE is similar or even higher than the United Kingdom.

Space-time clustering of CJD

The geographical distribution of cases of CJD by place of residence at death for the period 1st May 1990 - 30th April 1995 is shown in Figure 13. The method of Knox was used to look for evidence of clustering of cases of CJD in space and time (which might be interpreted as evidence for case-to-case transmission). Three hundred and nineteen cases in Great Britain, identified since 1984, were included in the analyses. Cases known to be iatrogenic or familial were excluded, as was one case from the Shetland Islands. When known, date of onset was used as the time point. When date of onset was unknown, it was set at 4 months prior to the date of death (4 months being the median duration from time of onset to time of death).

The results of the Knox analyses of these 319 cases are shown in Table 4. For most space-time combinations the observed number of pairs is very close to the number expected under the null hypothesis (no space-time clustering).

TABLE 4 **SPACE-TIME CLUSTERING OF DATES AND PLACES OF ONSET OF 319 CASES OF CREUTZFELDT-JAKOB DISEASE IN GREAT BRITAIN, 1985-APRIL 1995; OBSERVED AND EXPECTED NUMBERS OF PAIRS OF CASES WITH ONSETS WITHIN "CRITICAL" TIME AND SPACE DISTANCES OF EACH OTHER**

Time+ between dates of onset	Distance between places of residence at onset							
	< 5km		< 10km		< 20km		< 50km	
	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
<1 month	5	6.7	9	11.2	24	27.9	64	72.1
1-3 months	9	10.0	19	16.9	35	41.9	96	108.5
3-6 months	13	15.0	20	25.2	52	62.7	166	162.3
6-12 months	25	28.0	43	47.2	119	117.2	287	303.5
1-2 years	42	50.4	77	84.9	190	211.0	510	546.6
2-3 years	38	43.7	63	73.6	187	183.0	485	473.8
3-4 years	43	36.8	75*	62.0	156	154.0	401	398.9
4-5 years	37	31.6	61	53.2	125	132.3	316	342.5

\+ Critical times used were (in days): 35, 95, 185, 370, 735, 1100, 1465, 1830

* $p = 0.06$

Only one cell has excess observed pairs statistically significant at the 10% level. Seventy-five pairs were observed to occur within 10km of each other with onset 3 to 4 years apart (about 62 such pairs were expected). This slight excess is largely explained by a cluster of 16 cases (forming 26 pairs) in and around London. Given the number of space-time combinations tested (32), we should not be surprised to find a few cells significant at the 10% level in the absence of any clustering. The cluster observed may well have arisen through random variation.

An analysis of 588 cases of CJD occurring in Great Britain over the past 25 years (since 1970) is presented in Table 5. (During the period 1970 to 1984 only cases in England and Wales were recorded).

TABLE 5 **SPACE-TIME CLUSTERING OF DATES AND PLACES OF ONSET OF 588 CASES OF CREUTZFELDT-JAKOB DISEASE IN GREAT BRITAIN, 1970-APRIL 1995: OBSERVED AND EXPECTED NUMBERS OF PAIRS OF CASES WITH ONSETS WITHIN "CRITICAL" TIME AND SPACE DISTANCES OF EACH OTHER**

Time+ between dates of onset	Distance between places of residence at onset							
	< 5km		< 10km		< 20km		< 50km	
	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
< = 1 month	6	6.4	11	15.1	42	42.3	117	128.2
1-3 months	11	9.8	26	23.0	53	64.3	169	195.0
3-6 months	18	14.5	29	34.2	84	95.5	300	289.6
6-12 months	36*	28.0	69	65.8	208**	183.8	553	557.4
1-2 years	51	53.4	112	125.7	349	350.9	1023	1064.3
2-3 years	45	50.1	102	117.9	337	329.1	1043*	998.3
3-4 years	62**	46.0	114	108.3	311	302.3	938	916.9
4-5 years	53*	43.4	103	102.1	260	285.2	847	864.9
5-6 years	50	41.7	111	98.0	299*	273.7	847	830.2
6-7 years	37	39.1	91	91.9	248	256.6	785	778.3
7-8 years	45	38.2	97	89.8	269	250.6	785	760.2
8-9 years	37	34.0	75	79.9	220	223.1	698	676.7
9-10 years	28	35.7	75	84.0	238	234.6	740	711.7
10-15 years	102	127.8	288	300.7	804	839.4	2499	2546.0
15-20 years	52	67.9	190**	159.6	473	445.6	1357	1351.7

\+ Critical times used were (in days): 35, 95, 185, 370, 735,1100, 1465, 1830, 2195, 2560, 2925, 3285, 3655, 5490, 7310

* $0.05 <= p < 0.10$

** $0.01 <= p < 0.05$

There is little evidence of space-time clustering of cases in these data. At 6-12 months apart there was a small excess of pairs of cases at less than 5km apart and at less than 20km apart. However, there was no evidence of any excess either at a slightly shorter time interval (3-6 months) or at a slightly longer time interval (1 to 2 years). There was also a small excess of pairs occurring 2-3 years apart and within 50km of each other. At closer distances, however, there was no excess of pairs. At 3-4 years and 4-5 years apart there were small excesses of pairs within 5km of each other. At 5-6 years interval there was a small excess of pairs of cases within 20km of each other and at 15-20 years apart an excess of cases within 10km of each other. The finding of four clusters significant at the 10% level (1-sided) and 3 clusters significant at the 5% level (1-sided) is no more than we might expect in a table in which sixty different space-time combinations have been examined. The observed excesses of pairs cannot be interpreted as evidence of space-time clustering.

SECTION 2 CASE-CONTROL STUDY OF CJD

In addition to the descriptive epidemiological analyses, a case-control study of CJD has been carried out in the UK since May 1990. The methodology of this study parallels the previous case-control study of CJD carried out between 1980-1984 in England and Wales by Professor WB Matthews. Relatives of patients with suspect CJD are interviewed using a standard questionnaire, adapted from the previous study, which includes a wide range of questions relating to putative risk factors for CJD including occupational history and dietary history. For each index case a control is identified in the same hospital and is matched for sex and age $\pm$ 4 years. Cases with diseases which might be confused clinically with CJD are excluded. Where possible, a relative of the same degree is interviewed using the standard questionnaire and if this is not possible, the control is interviewed directly. Since May 1990 a relative of the control has been available in 59% and the control has been interviewed directly in 41%

Dietary history and risk of CJD

In last year's annual report, caveats relating to the dietary case-control study were stated in detail. In brief, the findings concerning dietary history are particularly difficult to interpret for a number of reasons:

1. The inevitably small number of cases included in the case-control study results in instability of data.
2. There is a potential misclassification of exposure as responses to the dietary case-control study are obtained from a relative rather than directly from the patient.
3. There is a substantial potential for response bias as respondents to the dietary case-control questionnaire are often aware of the hypotheses being tested.

In the Second Annual Report (1993), pudding consumption appeared to be the major dietary risk factor for Creutzfeldt-Jakob disease but it is of note that in last year's report and again in this year's report no significant association between pudding eating and risk of CJD has been observed. The major apparent dietary risk factor for CJD in last year's report was the consumption of veal with individuals reported to eat veal on average at least once a year

appearing to have over 13 times the risk of CJD in comparison with individuals who had never eaten veal. In this year's report the apparent relative risk of regular veal consumption has dropped to a factor of 4.06 and veal does not appear to be a risk factor at all when account is taken of potential confounding variables. These changes in apparent dietary risk factors for CJD from year to year underline the fragility of the apparent dietary associations, particularly in relation to relatively rare dietary exposures.

Analysis of relative risk from consumption of various products in suspect cases not subsequently confirmed to have CJD in last year's report provided strong circumstantial evidence of systematic recall bias. A similar analysis in this year's report provides further evidence of a systematic recall bias.

In this year's analysis, lifetime consumption of sweetbreads, brain, beef and venison are all associated with an apparent increase in the relative risk of CJD. However analysis of consumption of these and other animal products post-1985 when BSE was first identified shows no evidence for any increased relative risk of CJD. When account is taken of potential confounding variables, the only remaining apparent dietary risk factor for CJD is consumption of venison at least once per year. In view of the possibility of response bias and the very small numbers involved in the analysis of relative risk from venison, great caution should be taken not to over-interpret this finding.

One hundred and fifty cases of CJD identified between May 1990 and April 1995 (70%) were compared with age-, sex- and hospital-matched controls with regard to lifetime history of eating meat products. Consumption was recorded as follows: never, less than once per year, more than once per year but less than monthly, more than once per month but less than once per week, once per week or more, eaten but frequency unknown. For all cases and for 89 (59%) controls, information on dietary history was obtained from a relative. For the remaining 61 controls, information was obtained from the control themselves. In addition to collecting information on lifetime dietary history, dietary history since 1985 was also recorded. This information was available for 138 (92%) of case-control pairs. The analyses were performed using the computer package STATA and all estimates take account of individual matching.

The results of the comparison of 150 case-control pairs with regard to lifetime consumption of different types of meat is shown in Table 6. Evidence of dose-response relationships was sought by fitting the consumption categories described above (coded as 1, 2, 3, 4 and 5) as a continuous variable. It should

be noted that the two p-values for each type of meat are **not** independent of each other.

TABLE 6 RESULTS OF A COMPARISON BETWEEN 150 CASES OF CREUTZFELDT-JAKOB DISEASE, POST APRIL 1990, AND THEIR MATCHED CONTROLS WITH REGARD TO LIFETIME HISTORY OF EATING DIFFERENT TYPES OF MEAT

Type of product	Cons-umed	Number of cases (%)	Number of controls(%)	Odds Ratio	95% c.i.	p-value (OR = 1)	p-value (trend)
Lamb	No	1 (1)	8 (5)	1.0	-	0.04	0.02
	Yes	149 (99)	140 (95)	8.00	(1.07,355)		
Pork	No	0 (0)	2 (1)	1.0	-	0.50	0.22
	Yes	150 (100)	146 (99)	∞	(0.19,∞)		
Beef	No	0 (0)	1 (1)	1.0	-	1.00	0.02
	Yes	150 (100)	147 (99)	∞	(0.03,∞)		
Venison	No	101 (69)	125 (83)	1.0	-	0.004	0.003
	Yes	46 (31)	25 (17)	2.40	(1.31,4.38)		
Veal	No	96 (65)	114 (78)	1.0	-	0.02	0.007
	Yes	51 (35)	33 (22)	2.00	(1.10,3.64)		
Poultry	No	0 (0)	0 (0)	-	-	-	0.65
	Yes	148 (100)	148 (100)	-	-		
Fish	No	1 (1)	0 (0)	1.0	-	1.00	1.00
	Yes	148 (99)	147 (100)	0.00	(0.00,39.0)		

Pork, poultry and fish were consumed by almost all cases and controls. There was no evidence of any trend towards cases consuming these items more often than controls. Lamb and beef were also very widely consumed. Cases were reported to consume both of these meats more often than controls (test for trend; lamb, $p = 0.02$; beef, $p = 0.02$).

Consumption of venison and veal was much less widespread among both cases and controls. For both of these meats there was evidence that increasing frequency of consumption was associated with increasing risk of CJD (test for trend; venison, $p = 0.003$; veal, $p = 0.007$).

In order to investigate further the trends observed (for lamb, beef, venison and veal), the data were regrouped into the following categories:

- lamb and beef; less than monthly, at least monthly, weekly;
- venison and veal; never, less than yearly, yearly.

(Regrouping was performed because with the original five categories used the data were sparse).

Table 7 presents the results of an analysis of these data. There is evidence of an association between reported "regular" veal and venison eating and risk of CJD. Individuals reported to eat veal on average at least once a year appear to be at about 4 times the risk of individuals who have never eaten veal ($p=0.01$), while for venison there appears to be a twelve-fold increase in risk ($p=0.02$). There is, however, a very wide confidence interval around this estimate. There is no strong evidence that eating either veal or venison irregularly (less than once per year) is associated with increased risk of CJD ($p=0.40$ and $p=0.07$ respectively). Nevertheless, there is evidence of a dose response relationship between eating of both these meats and risk of CJD (tests for trend; veal, $p=0.006$; venison, $p=0.0006$).

TABLE 7 RESULTS OF AN ANALYSIS IN TRENDS IN CONSUMPTION OF LAMB, BEEF, VENISON AND VEAL BETWEEN CASES OF CREUTZFELDT-JAKOB DISEASE, POST APRIL 1990, AND THEIR MATCHED CONTROLS

Type of meat	Frequency of consumption	Number of cases (%)	Number of controls(%)	Odds ratio	95% c.i.	p-value (trend)
Lamb	< monthly	30 (20)	53 (36)	1.0	-	
	monthly	89 (60)	66 (45)	2.43	(1.35,4.38)	0.07
	weekly	29 (20)	28 (19)	1.69	(0.85,3.36)	
Beef	< monthly	10 (7)	25 (17)	1.0	-	
	monthly	62 (42)	63 (43)	2.38	(1.07,5.32)	0.01
	weekly	76 (51)	60 (41)	2.98	(1.33,6.69)	
Venison	never	101(69)	125 (83)	1.0	-	
	< yearly	33 (23)	23 (15)	1.81	(0.95,3.43)	0.0006
	yearly	12 (8)	2 (1)	12.41	(1.58,97.2)	
Veal	never	96 (65)	114 (78)	1.0	-	
	< yearly	32 (22)	25 (17)	1.37	(0.66,2.83)	0.006
	yearly	19 (13)	8 (5)	4.06	(1.35,12.19)	

There is also evidence of an association between regular eating of beef and risk of CJD, with those eating beef monthly or weekly experiencing a 2-3 fold increase in risk (monthly, $p=0.03$; weekly, $p=0.008$). A test for trend yields a statistically significant result ($p=0.01$) but it is not clear from the estimates of the odds ratio whether this reflects an underlying dose-response relationship or whether it simply reflects the increase in risk associated with regular eating.

The evidence for an association between lamb eating and risk of CJD is equivocal. Individuals eating lamb monthly appear to be at higher risk than those eating lamb less frequently ($p = 0.003$) but risk then appears to fall again. Thus the evidence for a dose-response relationship is unconvincing ($p = 0.07$).

These patterns remained largely unchanged when attention was restricted to case-control pairs for whom all data had been obtained from relatives (89 pairs). There was, of course, a tendency for the statistical significance of associations to be reduced with the smaller sample size. A summary of these data are presented in Table 8.

TABLE 8 RESULTS OF AN ANALYSIS OF TRENDS IN CONSUMPTION OF LAMB, BEEF, VENISON AND VEAL BETWEEN CASES OF CREUTZFELDT-JAKOB DISEASE, POST APRIL 1990, AND THEIR MATCHED CONTROLS, FOR THOSE PAIRS WITH DATA OBTAINED FROM RELATIVES

Type of meat	Frequency of consumption	Odds ratio
Lamb	< monthly	1.0
	monthly	2.01
	weekly	1.58
Beef	< monthly	1.0
	monthly	2.97
	weekly	4.36
Venison	never	1.0
	< yearly	2.42
	yearly	∞
Veal	never	1.0
	< yearly	1.59
	yearly	2.34

In addition to data on frequency of eating different types of meat, data were also collected on frequency of eating other animal "products". Table 9 presents a comparison of cases and controls with regard to lifetime consumption of these products.

TABLE 9 RESULTS OF A COMPARISON BETWEEN 150 CASES OF CREUTZFELDT-JAKOB DISEASE, POST APRIL 1990, AND THEIR MATCHED CONTROLS WITH REGARD TO LIFETIME HISTORY OF EATING VARIOUS ANIMAL PRODUCTS

Type of product	Cons-umed	Number of cases (%)	Number of controls(%)	Odds Ratio	95% c.i.	p-value (OR = 1)	p-value (trend)
Sausage	No	2 (1)	3 (2)	1.0	-	1.00	0.71
	Yes	144 (99)	146 (97)	1.50	(0.17,18.0)		
Tripe	No	99 (66)	98 (68)	1.0	-	0.68	0.89
	Yes	50 (34)	47 (32)	1.13	(0.65,1.95)		
Liver	No	16 (11)	18 (12)	1.0	-	0.58	0.96
	Yes	133 (89)	130 (88)	1.23	(0.59,2.56)		
Kidney	No	44 (30)	60 (41)	1.0	-	0.05	0.30
	Yes	103 (70)	88 (59)	1.67	(1.00,2.76)		
Sweet-breads	No	124 (86)	136 (93)	1.0	-	0.06	0.05
	Yes	20 (14)	11 (7)	2.25	(0.98,5.17)		
Tongue	No	58 (40)	70 (47)	1.0	-	0.19	0.86
	Yes	86 (60)	79 (53)	1.47	(0.82,2.64)		
Brains	No	123 (85)	141 (95)	1.0	-	0.02	0.07
	Yes	21 (15)	8 (5)	3.00	(1.19,7.55)		
Trotters	No	111 (76)	108 (74)	1.0	-	0.77	0.77
	Yes	35 (24)	38 (26)	0.92	(0.51,1.63)		
Puddings	No	56 (38)	69 (46)	1.0	-	0.10	0.73
	Yes	91 (62)	80 (54)	1.60	(0.92,2.80)		
Haggis	No	95 (65)	109 (73)	1.0	-	0.08	0.19
	Yes	51 (35)	40 (27)	1.65	(0.95,2.87)		
Heart	No	98 (68)	103 (71)	1.0	-	0.41	0.37
	Yes	47 (32)	42 (29)	1.26	(0.73,2.18)		

Almost all cases and controls were reported to have eaten sausage at some time and there was no evidence of any dose-response relationship. Only one case was reported ever to have eaten eyes. Similar proportions of cases and controls were reported to have eaten tripe and trotters, with no evidence of a dose-response relationship. Slightly more cases than controls were reported to have eaten liver, tongue and heart, but these differences were not statistically significant, nor was there any evidence of a dose-response relationship. More cases than controls were reported to have eaten puddings and haggis, but the evidence for these associations was weak ($p = 0.10$ and $p = 0.08$ respectively) and there was no evidence of a dose-response effect.

Higher proportions of cases than controls were reported to have eaten kidneys (p=0.05), sweetbreads (p=0.06) and brains (p=0.02). There was some evidence of a dose response relationship for sweetbreads (p=0.05) and brains (p=0.07), but not for kidneys (p=0.30).

Table 10 presents a more detailed analysis of the associations between lifetime consumption of kidneys, sweetbreads and brains, and risk of CJD, with consumption regrouped into 3 categories: never; less than once per year; once per year or more.

TABLE 10 RESULTS OF ANALYSIS OF TRENDS IN LIFETIME CONSUMPTION OF KIDNEYS, SWEETBREADS AND BRAINS BETWEEN CASES OF CREUTZFELDT-JAKOB DISEASE, POST APRIL 1990, AND THEIR MATCHED CONTROLS

Type of meat	Frequency of consumption	Number of cases (%)	Number of controls(%)	Odds ratio	95% c.i.	p-value (trend)
Kidneys	never	44 (31)	60 (42)	1.0	-	
	< yearly	26 (18)	20 (14)	2.04	(0.99,4.19)	0.08
	yearly	72 (51)	63 (44)	1.65	(0.96,2.83)	
Sweet-breads	never	124 (86)	136 (93)	1.0	-	
	< yearly	13 (9)	8 (5)	1.83	(0.68,4.96)	0.04
	yearly	7 (5)	2 (1)	3.50	(0.73,16.85)	
Brains	never	123 (86)	141 (95)	1.0	-	
	< yearly	15 (10)	6 (4)	2.79	(0.98,7.95)	0.03
	yearly	5 (4)	2 (1)	2.96	(0.55,15.85)	

Eating sweetbreads and brains were both associated with statistically significant trends, "regular" eating of either (once per year or more) being associated with about a three-fold increase in risk. The trend in the odds ratios was more apparent for sweetbreads than for brains, which suggested more of a "step-up" association. The evidence for an association between the eating of kidneys and risk of CJD was more equivocal. There was no clear trend in the estimates of the odds ratios, nor was there strong statistical evidence of a trend (p=0.08). Restricting attention to the subset of case-control pairs with exposure data obtained from relatives did not alter greatly this pattern of results.

Data on consumption of animal products post-1985 were available for 138 case-control pairs. There was no statistical evidence of an association between consumption since 1985 of any of the animal products listed in Table 9 and risk of CJD ($p > 0.10$ for all products). Nine cases compared with 4 controls were

reported to have eaten sweetbreads during this period (odds ratio = 2.67 [0.71,10.05], 3 cases and 3 controls were reported to have eaten brains (odds ratio = 1.00) and 84 cases compared with 70 controls were reported to have eaten kidneys (odds ratio = 1.41 [0.86,2.30]).

It is likely that many of the dietary exposures considered are associated in the population. For example, one might expect that individuals who eat a particular type of offal are more likely to eat other types than individuals who do not. Thus there is potential for major confounding of associations between dietary exposure and risk of CJD. In order to overcome this problem an attempt was made to model simultaneously the association between the different exposures identified above and risk of CJD. This was done by starting with a model including seven different items (lamb, beef, venison, veal, kidneys, sweetbreads, brains). Each of these items was fitted as a continuous variable with 3 levels of frequency (see Tables 7 and 10 above). From this model the least statistically significant item was dropped ($p > 0.05$) and the next model fitted. This process was continued until only items which were statistically significant simultaneously ($p < 0.05$) remained in the model. At the end of this procedure two items remained, both presenting strong evidence of a dose-response relationship with CJD; beef ($p = 0.01$) and venison ($p = 0.001$). Monthly consumption of beef was associated with a 2.3-fold increase in risk of CJD while weekly consumption was associated with a 3.2-fold increase. For venison the increase in risk was 1.9-fold for irregular consumption (< yearly) and 14.8-fold for more regular consumption.

In order to determine whether recall bias might be responsible for these observed associations, cases were compared with 51 individuals who had initially been identified as possible cases of CJD, whose relatives had been interviewed while CJD remained a possible diagnosis, but who were subsequently confirmed not to have CJD. (Thus we expect that this group will have been susceptible to any recall bias which might have affected the cases. Of these non-cases, 41% were pathologically confirmed not CJD, and 59% were classified on clinical grounds as not CJD (for example, a significant proportion of these cases made a complete clinical recovery).

Table 11 presents a comparison of the 150 confirmed CJD cases and these 51 "non-cases" with regard to their reported consumption of beef and venison. All evidence of a dose-response relationship between beef consumption and risk of CJD has disappeared, a finding consistent with the hypothesis that the association observed when cases were compared with their matched, non-suspect controls was due to recall bias. However, some evidence of an

increased risk of CJD associated with increasing consumption of venison remains.

TABLE 11 RESULTS OF ANALYSIS OF TRENDS IN LIFETIME CONSUMPTION OF BEEF AND VENISON BETWEEN 150 CASES OF CREUTZFELDT-JAKOB DISEASE, POST APRIL 1990, AND 51 "NON-CASES"

Type of meat	Frequency of consumption	Number of cases (%)	Number of "non-cases" (%)	Odds ratio	p-value (trend)
Beef	< monthly	10 (7)	2 (4)	1.0	0.46
	monthly	62 (42)	19 (40)	0.65	
	weekly	76 (51)	27 (56)	0.56	
Venison	never	101 (69)	40 (80)	1.0	0.08
	< yearly	33 (23)	9 (18)	1.45	
	yearly	12 (8)	1 (2)	4.75	

In summary, the dietary case-control study has demonstrated statistical associations between the risk of CJD and the lifetime history of consumption of a number of food products, from a number of different animal species. These apparent associations should be treated with great caution in view of the methodological problems with the case-control study including fragility of data and the possibility of recall bias. It is of note that the strong statistical association between a lifetime history of veal consumption and the risk of developing CJD in last year's report is much less apparent in this year's analysis and indeed the apparent risk from veal consumption is no longer significant when confounding variables are taken into account. It is also of note that there was no statistical evidence of an association between consumption of a variety of animal products post-1985 and risk of CJD. Analysis of the dietary case-control study in individuals identified as possible cases of CJD but in whom the diagnosis was subsequently not confirmed, continues to provide circumstantial evidence of recall bias.

In this year's analysis, the case-control study has demonstrated a strong statistical association between a lifetime history of venison consumption and the risk of developing CJD. This data is very fragile and rests primarily on a comparison of 12 cases who had a history of consumption of venison at least yearly in comparison with only 2 controls. It is also important to consider whether the statistical association is compatible with what is known of the biology of the spongiform encephalopathies. No case of spongiform encephalopathy has ever been identified in the deer population in the United Kingdom and there are no biological grounds for suspecting that venison

consumption should be a risk factor for CJD. It is likely that the apparent statistical association between venison consumption and the risk of CJD is either a chance finding or a product of recall bias.

Occupational history and risk of CJD

The occupational history of cases, controls and their spouses and their parents were also investigated to identify employment in the following areas: medical/nursing/dentistry, etc; laboratory work involving animals; work in pharmaceutical laboratories; work in other research laboratories; livestock farming/veterinary medicine; work in abattoirs/butchers' shops or other direct contact with animal carcasses; other occupations involving contact with animal products (eg leather workers).

There was no evidence that cases were more likely than controls to have worked in any of the above categories. Thirteen cases compared with 16 controls had worked in the medical professions; 9 cases compared with 13 controls had worked on farms/in veterinary medicine; 6 cases compared with 8 controls had worked in abattoirs/butchers' shops. One case had worked in an animal laboratory and one case had worked in a pharmaceutical laboratory (both pre- 1985). No other cases nor controls had ever worked in animal, pharmaceutical or other research laboratories. Slightly more cases than controls had worked in other occupations involving contact with animal products (14 versus 10; odds ratio = 1.57; $p = 0.48$).

Nor was there any convincing evidence that spouses or parents of cases were more likely to have worked in any of these occupations than those of controls.

Most cases (143) and controls (145) had been married at some point in their lives. There was no evidence that cases were more likely than controls to have had spouses who worked in the medical professions (6 cases, 7 controls) or farming (4 cases and 6 controls). No cases or controls had spouses who had worked in animal laboratories. One case and 1 control had spouses who had worked in pharmaceutical laboratories while one case had a spouse who had worked in a research laboratory. Seven cases compared with two controls had spouses who had worked in abattoirs/butchers' shops (odds ratio = 6.0, $p = 0.12$) while 5 cases compared with 2 controls had spouses who had worked in other occupations involving contact with animal products (odds ratio = 2.50, $p = 0.45$).

Similar patterns were observed with regard to the occupations of parents of cases and controls. No cases or controls had parents who had worked in any kind of laboratory. Four cases and 4 controls had parents who had worked in the medical professions while 13 cases and 15 controls had parents who had worked in farming/veterinary medicine. Six cases compared with 2 controls had parents who had worked in abattoirs/butchers' shops (odds ratio = 5.0, p = 0.22) while 4 cases but no controls had parents who had worked in other occupations involving contact with animal products (p = 0.13).

CJD has previously been described in two dairy farmers who had had BSE in their herds. A third case of CJD in a dairy farmer with a similar potential occupational exposure has now been identified and a case report has been submitted for publication. The occurrence of 3 such cases over the first 5 years of the study is clearly a matter of concern. However, the clinicopathological features in all 3 cases were compatible with sporadic CJD and no mechanism of cross contamination has been identified in any of these cases. Analysis of occupation at diagnosis in sporadic CJD in the UK (Table 12) demonstrates a wide range in apparent risk of CJD in relation to occupation including an increased apparent risk in occupations with no obvious increased risk in relation to BSE.

TABLE 12 OCCUPATION AT DIAGNOSIS IN SPORADIC CASES (1990-1995*)

Occupation	Number of cases	Incidence/Million**
Managers	14	0.3
Secretary/Clerical	10	0.5
Shop workers	7	1.7
Medical/Paramedical	6	5.7
Farmer	3	4.1
Teacher	3	0.7
Professional driver	3	8.2
Vicar	2	11.8
Journalist	1	2.5
Abattoir worker/butcher/vet	0	0

* n = 169

** Incidence figures do not take into account proportion of total population in employment (46%) or proportion of patients retired from employment (43%).

Analysis of the relative risk in farmers in Europe has demonstrated a similar relative risk to this particular occupational group in a number of countries in Europe (Table 13). This does not suggest that there is any additional risk factor for CJD to farmers in the United Kingdom in relation to countries which are either BSE free or which have had only a very small number of cases.

TABLE 13 THE INCIDENCE OF CJD IN "FARMERS" IN EUROPE

Country	Year	Ever Employed in Farming	Incidence cases per million farmers	Employed in farming at diagnosis	Incidence - Denominator All Farmers	Incidence - Denominator Dairy Farmers
France	1992	4		1		
	1993	5	2.7	1	0.72	4.8
	1994	6		2		
Germany	Oct93-94	6	2.7	2	0.90	3.8
Italy	1993	6	1.1	3	0.57	13.6
Netherlands	1993	1	3.4	0	0	0
	1994	1		0		
UK	1990	0		0		
	1991	1		0		
	1992	5	3.5	1	0.91	5.7
	1993	3		1		
	1994	2		1		

This table is adapted from the Yearly Activity Report on CJD surveillance in the European Community (1994).

BIOMED1 project for the surveillance of CJD in the European Community

National surveillance projects for CJD have been established in France (project co-ordinator Dr A. Alperovitch, INSERM U.360, Hôpital de La Salpêtrière, 75651 Paris Cedex 13, France), Germany (project co-ordinator Dr T. Weber, Klinik und Poliklinik fur Neurologie, University of Gottingen, Robert-Koch-Straβe 40, 37075 Gottigen, Germany), Italy (project co-ordinator Professor M. Pocchiari, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Roma, Italy), the Netherlands (project co-ordinator Professor A. Hofman, Department of Epidemiology and Biostatistics, Erasmus University Medical School, PO Box 1738, 3000 DR Rotterdam, The Netherlands), Slovakia (project co-ordinator Dr E. Mitrova, The Institute of Preventative and Clinical Medicine, Limbova 14, Bratislava, Slovakia) and the UK. A grant from the European Community was awarded in 1993 in order to co-ordinate these surveillance projects which now share common diagnostic criteria, methodologies and case-control questionnaire. The incidence of CJD in participating countries is similar, both in 1993 and 1994 (Table 14).

There is therefore good evidence that up to 1994 there has been no significant change in the incidence of CJD in the UK in comparison to other countries within Europe (and also elsewhere, including New Zealand).

TABLE 14 INCIDENCE OF CJD IN THE EUROPEAN COMMUNITY

	France	Germany	Italy	Netherlands	UK
TOTAL (number of definite & probable cases)					
1993	41	21*	40	14	41
1994	47	58	30	16	54
INCIDENCE (cases/million persons years)					
1993	0.73	0.53	0.70	0.90	0.71
1994	0.81	0.73	0.53	1.04	0.93

* July - December only

A case-control study of risk factors for CJD has been carried out in participating countries in Europe since 1993. A preliminary analysis was carried out in May 1995 and the final analysis will be available in early 1996. The case-control study may provide important comparative information on relative risk factors for CJD in participating countries.

An application to continue the European CJD Surveillance Project was made to the BIOMED2 programme but was unfortunately unsuccessful.

CJD in an adolescent

Comment was made in the last report regarding a case of suspect CJD in an adolescent. The diagnosis in this individual remains uncertain and may depend on eventual histological examination of the brain. It is unusual for patients with CJD to survive for longer than 12 months.

The diagnosis of CJD has recently been confirmed in a 19-year old individual and detailed investigations are currently in progress (this case is not included in the overall analysis for this year's annual report as the patient was identified after April 30th, 1995). The occurrence of CJD in a patient of this age is exceptional but not without precedent (see: Possible Creutzfeldt-Jakob disease in an adolescent. Weekly Epidemiological Record 1994; 15: 105-112). CJD

has been described previously in 2 adolescents in the United States of America which is free of BSE and in one adolescent in France which was free of BSE at the time of the patient's clinical illness. It would therefore be premature to conclude that the occurrence of CJD in an adolescent in the United Kingdom was indicative of transmission of BSE.

Conclusions

The national surveillance programme for CJD in the United Kingdom was initiated in May 1990. The information provided in this report continues to provide evidence of a high level of case ascertainment and that detailed clinical and epidemiological information has been obtained in the great majority of patients. A high post mortem rate has been maintained through the period of the study. The success of the project continues to depend on an extraordinary level of co-operation from the Neuroscience Community and other medical and paramedical staff throughout the United Kingdom. We are particularly grateful to the relatives of patients for their help with the study.

Over a period of 25 years, the number of cases of CJD identified annually has increased. The major increase has been since 1990 and in 1994 the incidence of CJD was higher than in any previous year. It is impossible to say with certainty to what extent these changes reflect an improvement in case ascertainment and to what extent, if any, changes in incidence. Analysis demonstrates that the major influence in the increased incidence of cases is an increased number of cases of CJD in those aged 75 and over, although in 1994, there was also an increase in the numbers of cases aged under 75. It is however of note that the overall incidence figures for CJD in the United Kingdom are comparable to other countries in Europe and elsewhere in the world, including countries which are free of BSE.

There is no strong evidence of changes in the geographical distribution of CJD between the periods 1970-1984 (pre-BSE) and 1985-1995 (post-BSE). Previous analysis found no convincing evidence of space-time clustering during the earlier period and we have not found any convincing evidence of space-time clustering in the later period.

Analysis of occupational histories has revealed no evidence that any of the occupations considered on biological grounds as theoretically carrying a risk of CJD were actually associated with an increased risk of CJD. The occurrence of CJD in 3 dairy farmers with potential exposure to BSE is clearly a matter of concern. It is of note that occupations with no apparent increased biological risk in relation to CJD have a higher incidence than farmers in the United

Kingdom and that the incidence of CJD in farmers in continental Europe is similar to the United Kingdom. This does not suggest that there is any additional risk factor for CJD to farmers in the United Kingdom in relation to other countries.

Analysis of dietary histories has revealed statistical associations between various meats/animal products and risk of CJD. The strongest of these associations statistically was with the consumption of venison. It is of note that the strongest of the statistical associations in last year's report was veal eating and that this is no longer apparently a major dietary risk factor for CJD. This underlines the difficulties with the interpretation of the dietary case-control study and suggests that any positive findings should be treated with caution.

The combined study of CJD in the European Community funded through the BIOMED1 programme has provided extremely important information in relation to the comparative risk of CJD in countries with or without BSE. The case-control study may provide further important information on a comparison of risk factors, including dietary exposures, in participating countries in Europe. It is inevitable that systematic surveillance of CJD will result in the identification of a wide spectrum of cases with CJD, for example cases at the extremes of the expected age range and cases with minimal or maximal pathology. It is also inevitable that by chance individual cases will be identified which have a potential theoretical link with BSE, for example through occupation. It may be impossible, on the basis of epidemiological evidence, to reach any conclusion as to the significance of such cases and it is important to have comparative background information from other countries in order to determine whether any unusual case in the United Kingdom has such atypical features as to suggest a new form of human spongiform encephalopathy. It is also important to consider whether any other scientific research, for example transmission studies, is likely to provide further information on aetiology in any specific case.

The incidence of CJD in the United Kingdom has risen significantly since 1990. Comparison with the incidence in other countries suggests that this rise in incidence is most likely to be related to improved ascertainment of cases. Other analyses including the case-control study do not provide any conclusive evidence of a change in CJD that can be attributable to BSE. The identification of CJD in 3 dairy farmers with a potential occupational exposure to BSE and the occurrence of CJD in a teenager reinforces the importance of continuing careful surveillance of CJD with particular reference to occupational risk and age incidence.

SECTION 3 FIGURES

DEATHS FROM CREUTZFELDT-JAKOB DISEASE IN ENGLAND AND WALES
1ST JANUARY 1970 - 30 APRIL 1995

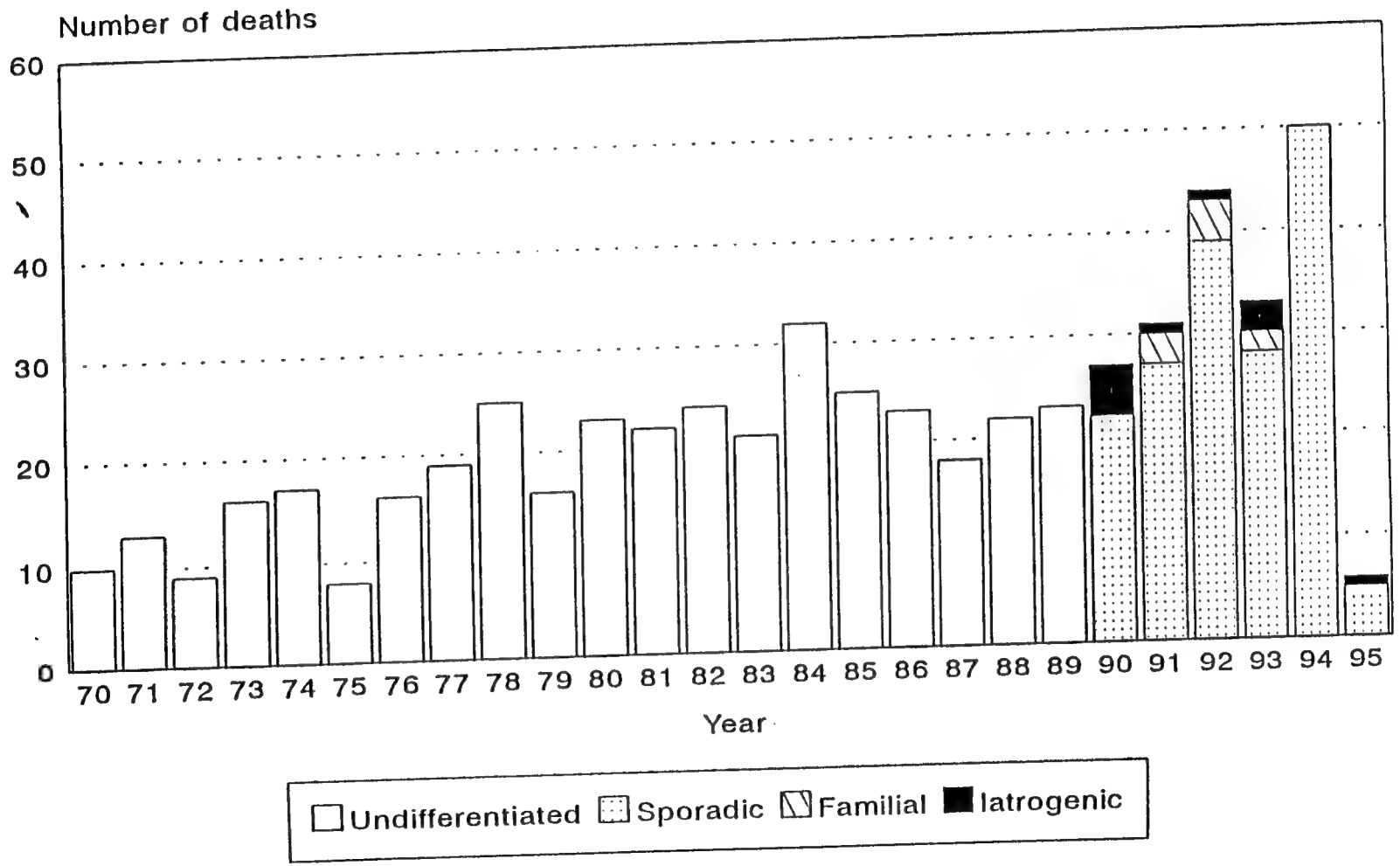


FIGURE 1

DEATHS FROM CREUTZFELDT-JAKOB DISEASE
IN SCOTLAND, NORTHERN IRELAND AND THE CHANNEL ISLANDS
1ST JANUARY 1985 TO 30TH APRIL 1995

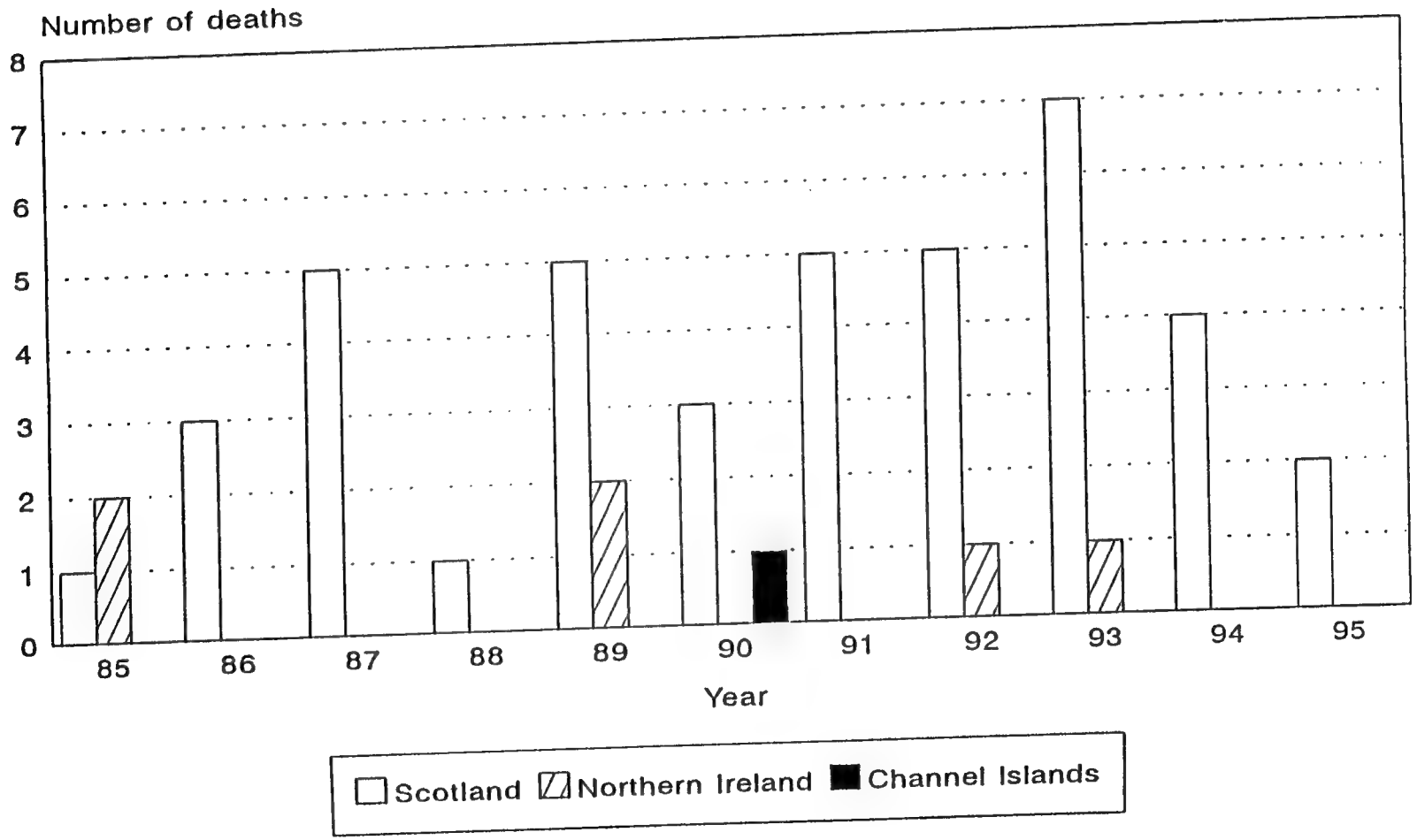


FIGURE 2

FIGURE 3

AGE- AND SEX-SPECIFIC MORTALITY RATES
FROM CREUTZFELDT-JAKOB DISEASE
ENGLAND AND WALES, 1970-1979

FIGURE 4

AGE- AND SEX-SPECIFIC MORTALITY RATES
FROM CREUTZFELDT-JAKOB DISEASE
ENGLAND AND WALES, 1980-1984

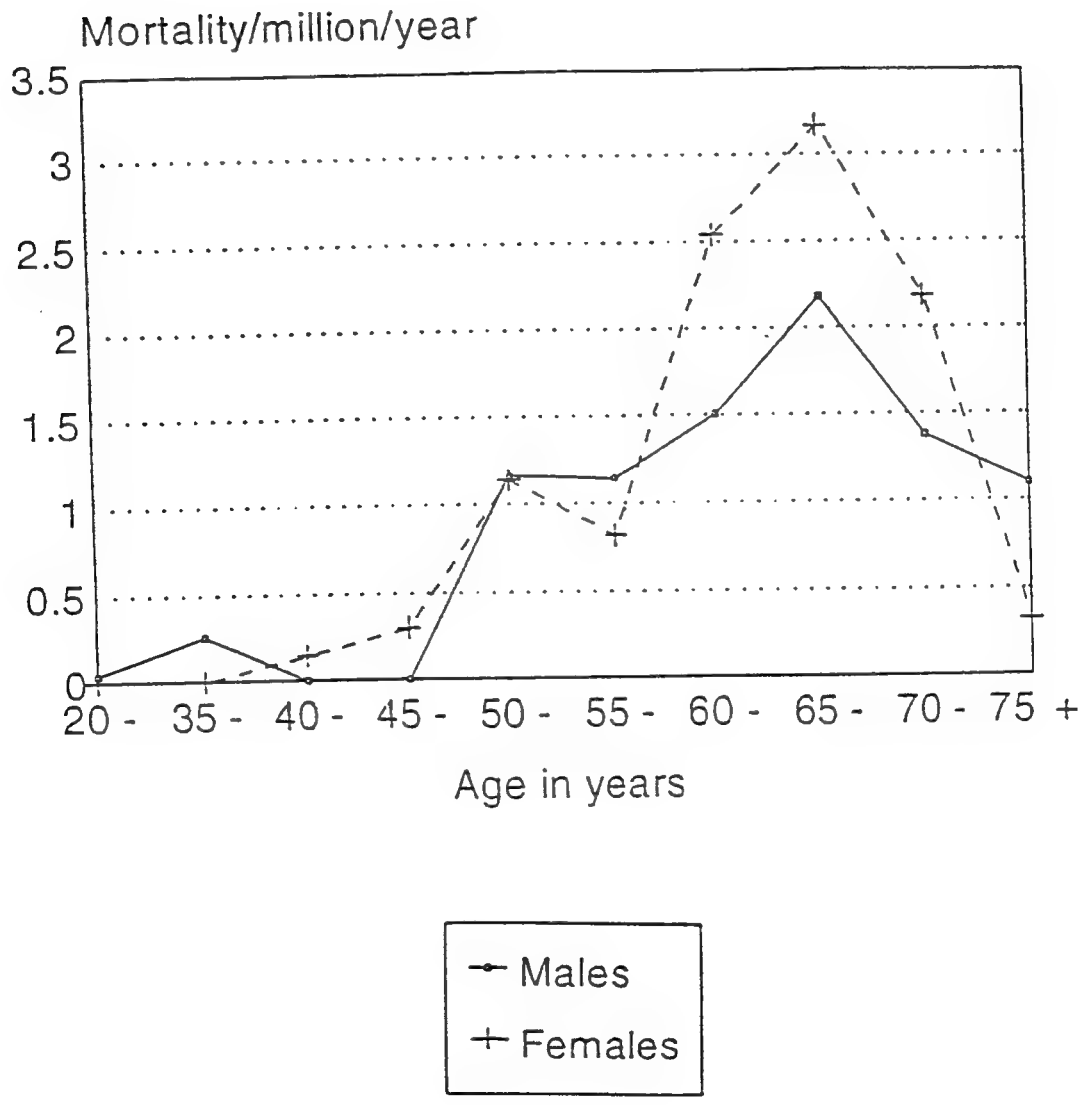


FIGURE 5

AGE- AND SEX-SPECIFIC MORTALITY RATES
FROM CREUTZFELDT-JAKOB DISEASE
GREAT BRITAIN, 1985-1989

FIGURE 6

AGE- AND SEX- SPECIFIC MORTALITY RATES
FROM CREUTZFELDT-JAKOB DISEASE
GREAT BRITAIN, 1990 TO 30TH APRIL 1995

FIGURE 7

MORTALITY BY COUNTY, 1970-1984

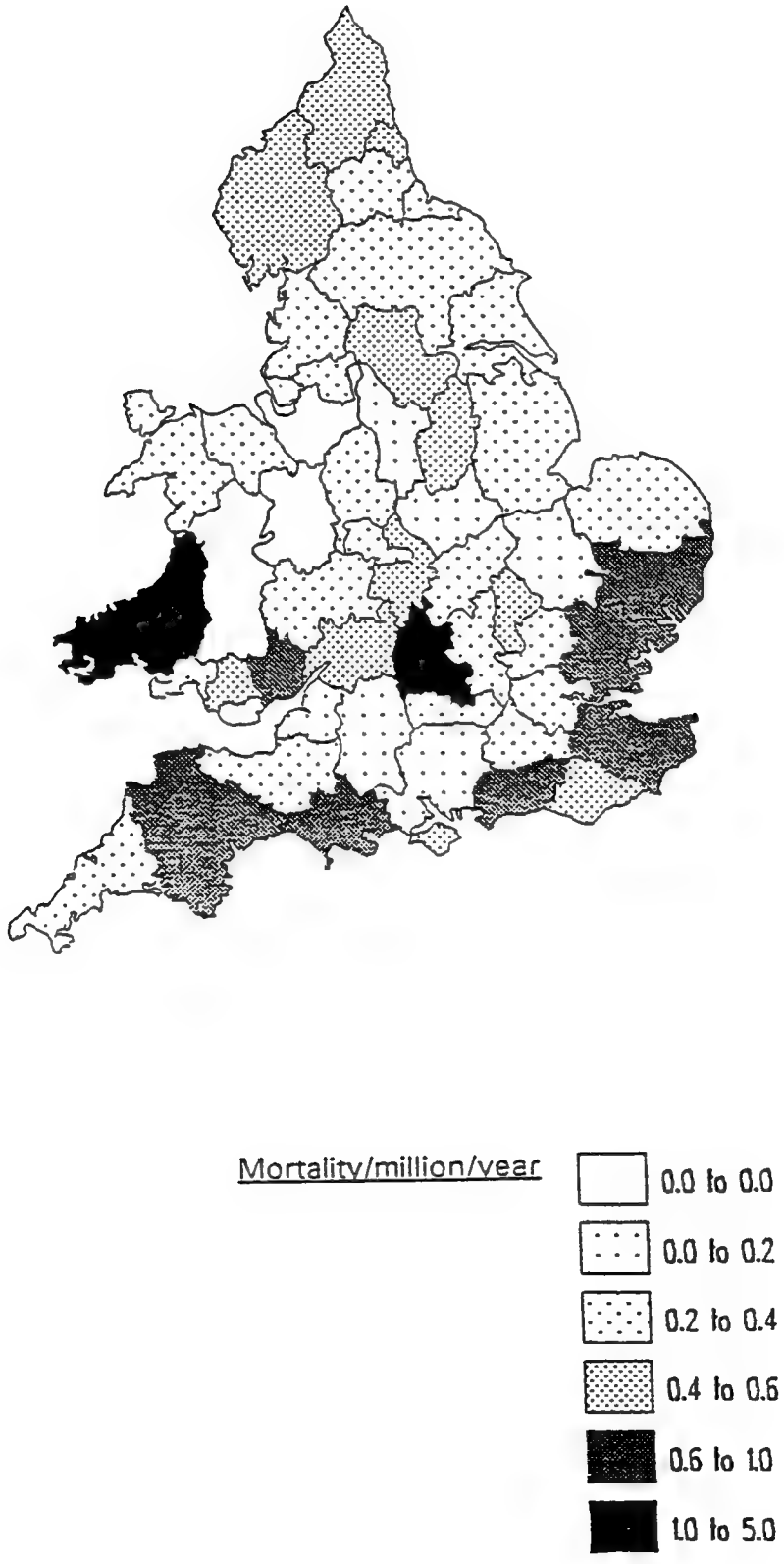
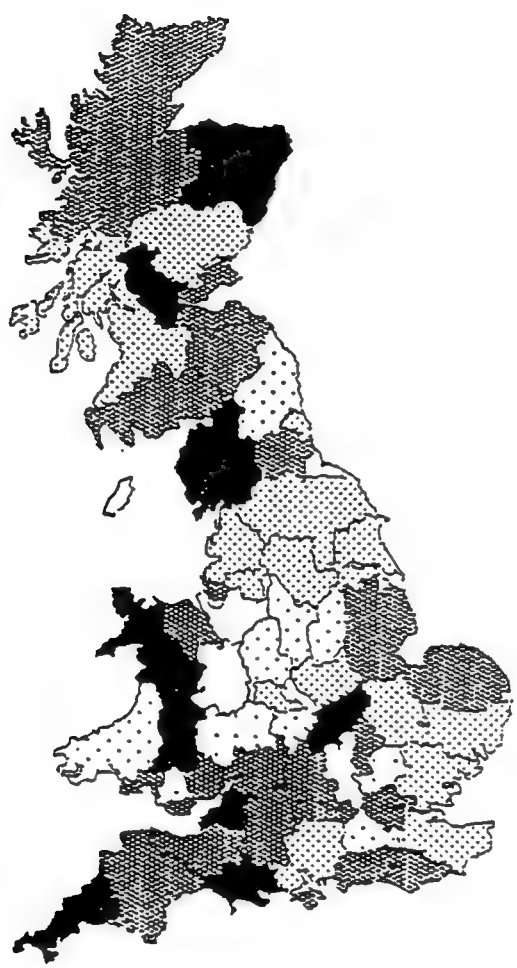


FIGURE 8

MORTALITY BY COUNTY, 1985-1994

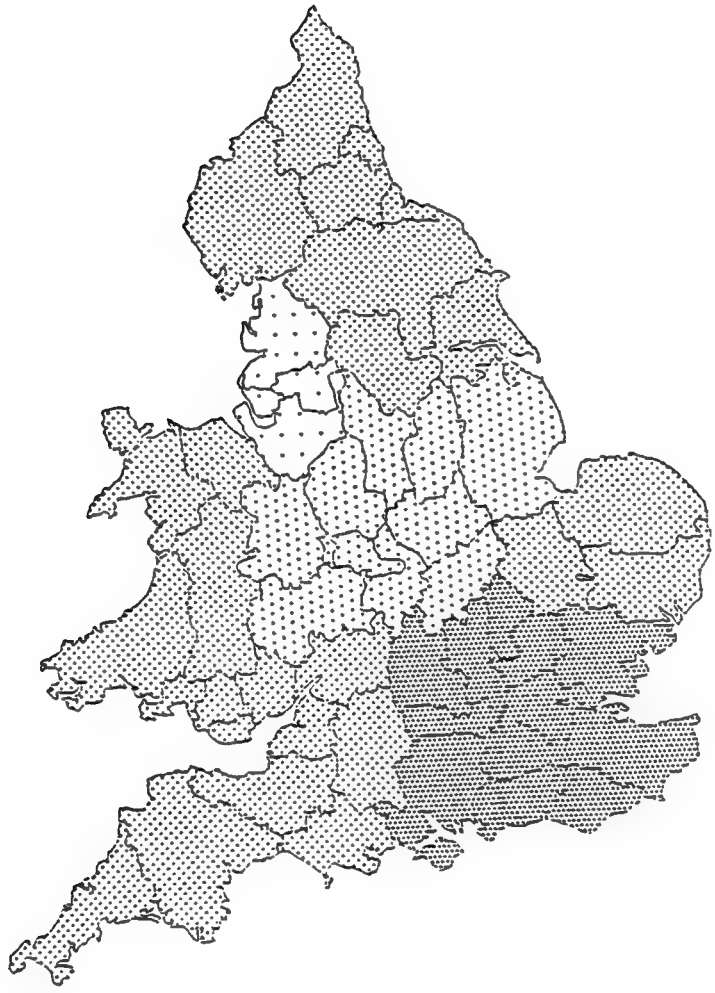


Mortality/million/year

- 0.0 to 0.0
- 0.0 to 0.2
- 0.2 to 0.4
- 0.4 to 0.6
- 0.6 to 1.0
- 1.0 to 5.0

FIGURE 9

SMRs BY STANDARD REGION IN ENGLAND AND WALES, 1970 TO 1984



SMR

50 to 70

70 to 90

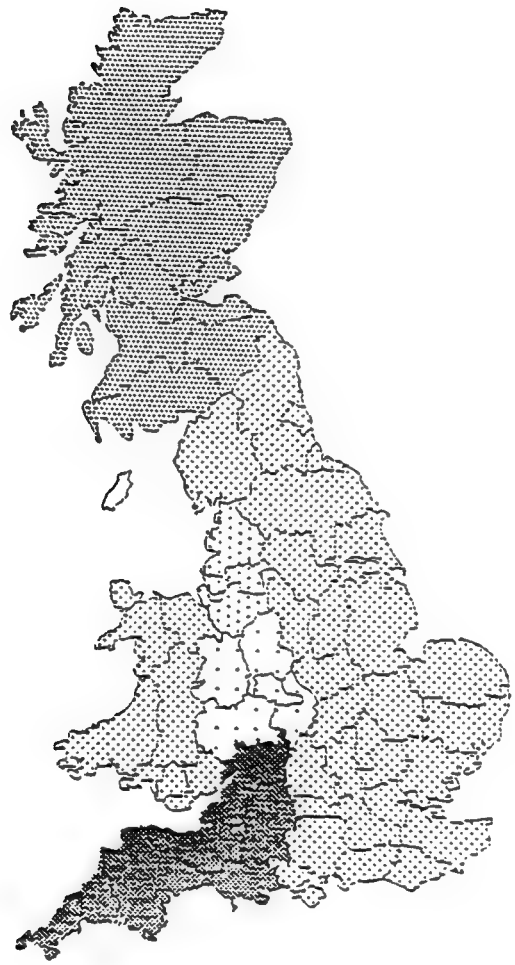
90 to 110

110 to 130

FIGURE 10

SMRs BY STANDARD REGION IN GREAT BRITAIN,

1985 TO 1994



SMR

50 to 70

70 to 90

90 to 110

110 to 130

130 to 150

SPORADIC CJD
DEATHS FROM 1980-1994
UNDER 75 YEARS OF AGE

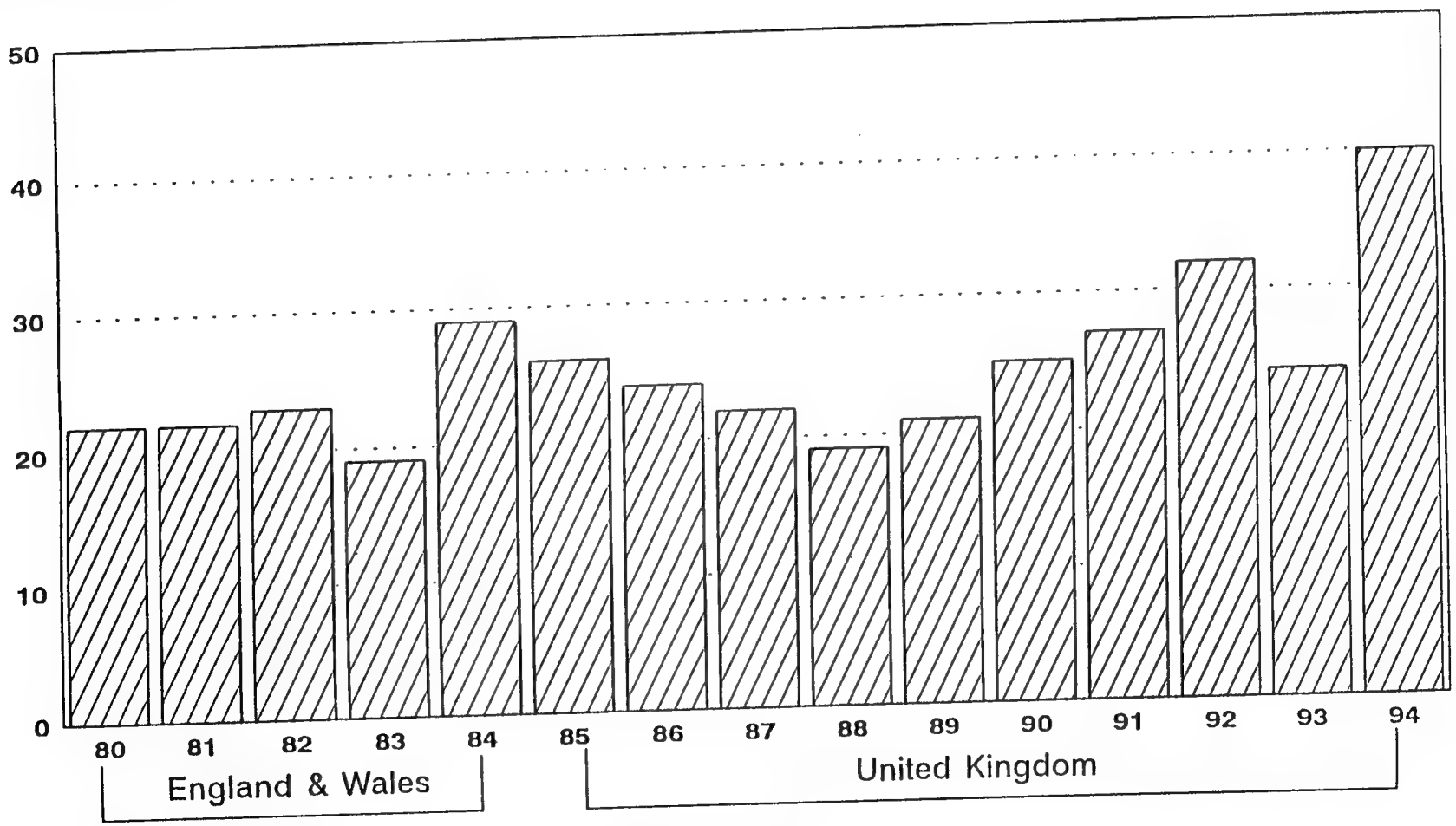


FIGURE 11

SPORADIC CJD
DEATHS FROM 1980-1994
75 YEARS OF AGE AND OVER

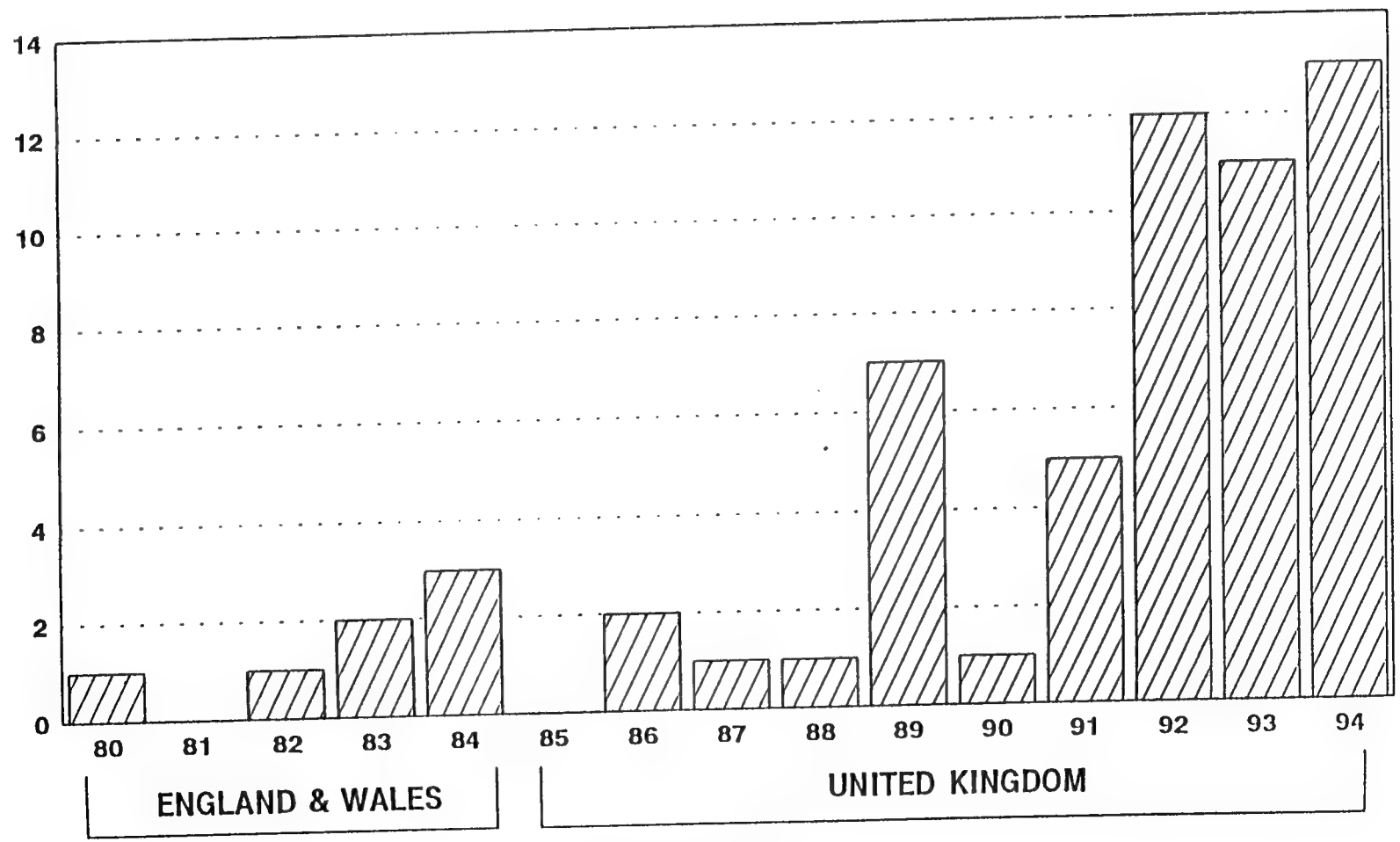
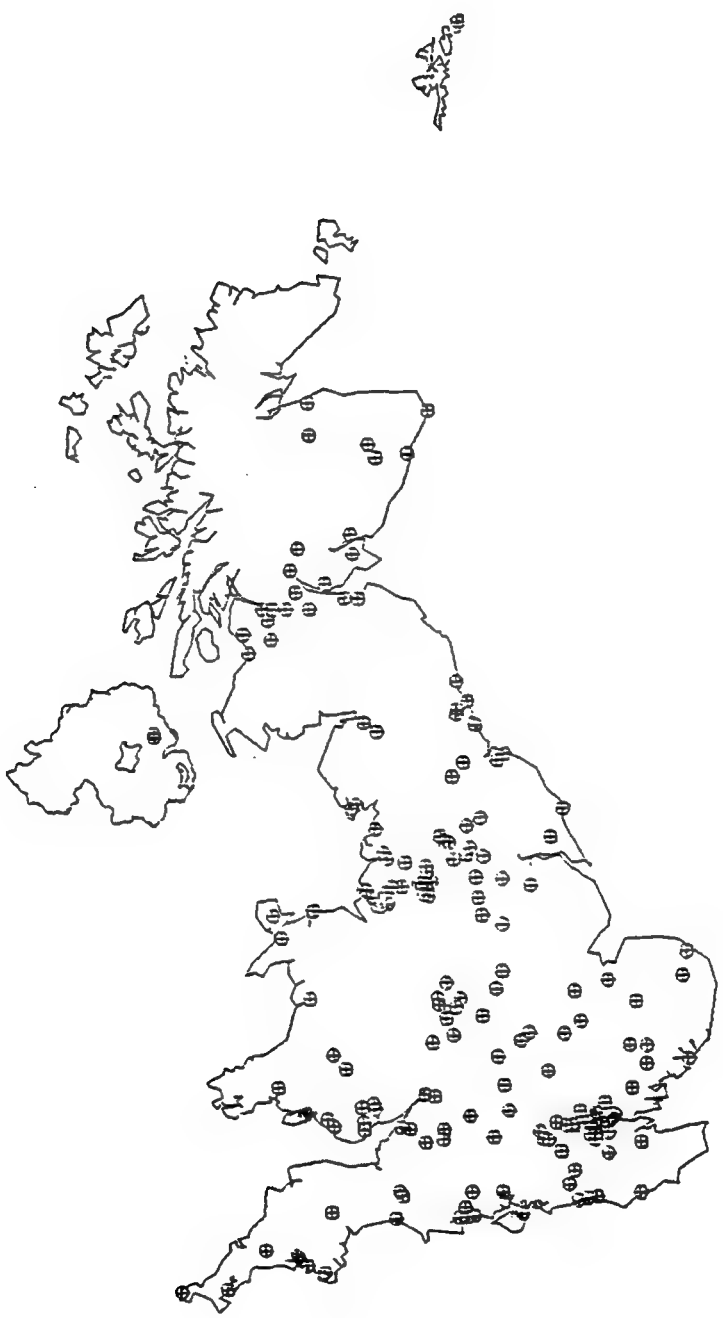


FIGURE 12

FIGURE 13

CREUTZFELDT-JAKOB DISEASE IN THE UNITED KINGDOM
DEFINITE AND PROBABLE CASES (1 MAY 1990 - 30 APRIL 1995)



SECTION 4 NEUROPATHOLOGICAL VALIDATION

Statement of Progress.

The 4th year of the neuropathology project has continued the work of detailed neuropathological examination on cases referred to the Unit for full autopsy, or following autopsy elsewhere in the country. Much effort is put into attempting to secure autopsy on suspected cases of CJD, with widespread dissemination of autopsy protocols to other pathologists in UK. Formal collaborations with other neuropathologists in UK (particularly Dr J.M. McKenzie, Liverpool and Dr J. McLaughlin, London) have continued to ensure that a high autopsy rate is secured. The contribution of other pathologists throughout UK is recognised in this respect, both for autopsies on clinically suspected cases of CJD and in the referral of cases in which the diagnosis is suspected on histological grounds in the absence of a secure clinical diagnosis.

The neuropathologists working on the project (Dr J.W. Ironside and Dr J.E. Bell) are now supported by 2 full-time MLSO 2, a part-time secretary and an administrative secretary/data manager. The contract for the neuropathological surveillance project was renewed in January 1995; this included the appointment of new staff at MLSO 2 level and administrative secretary/data manager in order to cope with the increasing workload in the laboratory, to ensure accurate information is stored on each case and that full compatibility with the clinical database is maintained. These 2 new appointments are for 1 year in the first instance, but continuation of employment for the following 3 years of the contract is anticipated.

Surveillance and Workload During 1994/95.

A detailed breakdown of the workload of the laboratory is summarised on Table 15 for 1st May 1994 - 30th April 1995. The overall figures for human tissues shows a continued increase from previous years. A slight increase in the number of non-CJD cases has been noted, particularly the category of organic dementia other than Alzheimer's disease. In addition to the sporadic CJD cases, the laboratory has examined a case of growth-hormone associated iatrogenic CJD, one case of Gerstmann-Straussler-Scheinker syndrome, one case of fatal familial insomnia and a cortical biopsy which was suggestive of CJD although the histological features were not entirely characteristic. The

patient concerned has subsequently died and an autopsy has been performed in the Frenchay Hospital, Bristol. Material from this case will be examined fully in the CJD laboratory. Samples of umbilical blood and cord have been obtained from an infant whose mother is suffering from suspect iatrogenic CJD related to a previous human dura mater graft.

Prion Protein Immunocytochemistry.

The CJD unit laboratory is recognised as a leading international centre in this field; this technique is of both research and diagnostic value, particularly in cases of suspected CJD in which only limited histological material is available, or where the classical histological features are absent. Details of scientific publications in this field are included in the relevant Appendix; many of the antibodies used in the laboratory are obtained from scientific colleagues in UK and we are particularly grateful to Dr J. Hope and his staff at the MRC/BBSRC Neuropathogenesis Unit, Edinburgh and Dr C. Birkett and colleagues at IAH, Compton.

Heath and Safety

The CJD Unit laboratory also provides advice on a wide range of health and safety issues concerning the handling of CJD tissues. Dr J.E. Bell is a member of the ACDP working party whose guidelines were published earlier this year (Precautions for Work with Human and Animal Transmissible Spongiform Encephalopathies; HMSO). The publication of the revised ACDP guidelines on this matter have clarified the concerns of many medical and laboratory staff, but interpretation in specific instances is frequently requested. Detailed safety protocols are constantly updated in the light of current information and are widely disseminated to other workers in the field.

Tissue Handling and Storage.

The CJD Unit laboratory houses a large tissue and organ bank which is used for research purposes by workers in the Unit, and is also available to other workers on collaborative projects in UK, Europe and USA. The appointment of a database manager/administrative secretary will assist the work of the tissue and organ bank, and also provide additional detailed information which is used in the analysis of neuropathological information in the surveillance project.

Research Activities

Research activities in neuropathology are undertaken under the auspices of the MRC and BBSRC, which support 2 post-doctoral scientists (Dr I. Goodbrand and Dr K. Sutherland) and a MLSO 1. The investigative projects are based on clinical neuropathology, and focus on the distribution of prion protein in the central nervous system in CJD, and the automatic recognition and analysis of specific neuropathological features in CJD using a computer-based system. The CJD Unit laboratory had earlier hosted a MCR workshop on prion protein immunocytochemistry; a consensus report has now been completed for this study and is likely to become a landmark document. The MRC - funded project has recently identified subsets of CJD based on PrP localisation and classical neuropathology; these are expected to throw light in the mode of entry and likely spread of the infective agent within the central nervous system.

BIOMED1 Project on CJD in the European Community.

Dr Ironside is involved in the BIOMED1 Concerted Action on CJD surveillance as a reference pathologist, and has participated in a joint project to publish criteria for the laboratory diagnosis of CJD. Dr Ironside is also involved in the BIOMED1 project on the neuropathology of CJD (Chairman Professor H. Budka, Vienna) with whom joint projects have been undertaken to establish criteria for tissue handling, tissue sampling and neuropathological diagnosis. The UK surveillance project is recognised as a leading centre in this project and continues to generate much interest from other EU countries, This has resulted in the submission of a number of cases for diagnostic opinion (see below); the role of the unit as an EU reference centre may increase in the future.

Laboratory Visitors.

A large numbers of visitors came to the surveillance unit laboratory during 1994/95 including neuropathologists, clinicians, scientists and technical staff. Many of these individuals have been concerned with the issues of tissue handling and safety protocols, and the establishment and organisation of the tissue and organ banks.

Media Contacts

Dr Ironside and Bell are frequently contacted by the press and broadcasting companies for clarification and comment on issues relating to BSE and risk to human health. More specific comments are requested on matters concerning the neuropathology of CJD, the importance of obtaining neuropathological

verification of the diagnosis on suspected CJD cases, and current investigative techniques.

Organisations interested in CJD

Dr Ironside has attended meetings held under the auspices of the Meat and Livestock Commission and to present data concerning the neuropathology of CJD and its relationship to BSE.

TABLE 15

NEUROPATHOLOGY OF CREUTZFELDT-JAKOB DISEASE
1 MAY 1994 - 30 APRIL 1995

98 CASES (100 SPECIMENS)

ANIMAL TISSUES	HISTORICAL CJD CASES (PRE-1990)	CASES REFERRED FROM EU COUNTRIES	SUSPECTED CJD CASES
19	5	10	64

GROWTH HORMONE ASSOCIATED CJD	GSS	FFI	CORTICAL BIOPSY OF SUSPECTED CJD	CONFIRMED CJD	ALZHEIMER'S DISEASE	OTHER ORGANIC DEMENTIAS	OTHERS
1	1	1	1	34	7	8	11

Pick's disease	2	Encephalomyelitis	1
Dementia in MND	2	Hypoxia/ischaemia	4
Lewy body disease	3	Intravascular B cell lymphoma	1
Multisystem atrophy	1	Metastatic carcinoma	1
		CSF (normal)	2
		Negative cortical biopsy	2

SECTION 5 PUBLICATIONS

Dr T.F.G. Esmonde, Research Registrar at the CJD Surveillance Unit 1990-1992, submitted a thesis to the Trinity College University of Dublin entitled "Surveillance of Creutzfeldt-Jakob Disease". In June 1995, Dr Esmonde was awarded the degree of M.D.

1. Will RG. Prion Disease. Lancet 1990; 336: pp369.

2. Will RG. Subacute spongiform encephalopathies. In: Current Medicine 3, Ed. D.H. Lawson, Published: Churchill Livingston, Edinburgh. 1991; Chapter 9 pp 127-143.

3. Will RG. Comment: Slow virus infection of the central nervous system. Current Medical Literature (Neurology), 1991 Volume 7, Number 3, September 1991, pp 67-69.

4. Will RG. An overview of Creutzfeldt-Jakob disease associated with the use of human pituitary growth hormone. Develop. Biol. Standard 1991; Vol 75: 85-86.

5. Will RG. Is there a potential risk of transmission of BSE to the human population and how may this be assessed? In: Subacute Spongiform Encephalopathies - Proceedings of a Seminar in the CEC Agricultural Research Programme held in Brussels, 12-14 November 1990. Eds: R. Bradley, M. Savey & B. Marchant. Published by Kluwer Academic Publishers 1991.

6. Will RG. Epidemiological surveillance of Creutzfeldt-Jakob disease in the United Kingdom. Eur. J. Epidemiol. 1991; 7(5): 460-465.

7. Will RG. The spongiform encephalopathies. JNNP 1991; 54(9): 761-763.

8. Esmonde TFG, Will RG. Magnetic resonance imaging in Creutzfeldt-Jakob disease. Ann. Neurol. 1992; 31(2): 230.

9. Brown P, Preece MA, Will RG. 'Friendly fire' in medicine: hormones, homografts and Creutzfeldt-Jakob disease. Lancet 1992; 340: 24-27.

10. EsmondeTFG, Will RG. Transmissible Spongiform Encephalopathies and their Relationship to Human Neurodegenerative Disease. British Journal of Hospital Medicine 1992; 49(6): 400-404.

11. Will RG, Esmonde TFG, Matthews WB. Creutzfeldt-Jakob Disease Epidemiology. In: Prion Diseases of Humans and Animals. Eds: Prusiner SB, Collinge J, Powell J, Anderton B. 1992; ppp 188-199.

12. Esmonde TFG, Will RG. Creutzfeldt-Jakob disease in Scotland and Northern Ireland 1980-1989. Scottish Medical Journal 1992; 37: 181-184.

13. Scott PR, Aldridge BM, Clarke M, Will RG. Bovine spongiform encephalopathy in a cow in the United Kingdom. JAVMA 1989;195; 1745-1747.

14. Will RG. BSE and the spongiform encephalopathies. In: Recent Advances in Clinical Neurology. Ed: Kennard C. 1992; Chapter 5, pp 115-127.

15. Esmonde TFG, Will RG, Slattery JM, Knight R, Harries-Jones R, de Silva R, Matthews WB. Creutzfeldt-Jakob Disease and Blood Transfusion. Lancet 1993;341: 205-207.

16. Esmonde TFG, Lueck CJ, Symon L. Duchen LW, Will RG. Creutzfeldt-Jakob Disease and Lyophilised Dura Mater Grafts: Report of Two Cases and a Review of the Literature. JNNP 1993; 56: 999-1000.

17. Sawcer SJ, Yuill GM, Esmonde TFG, Estibeiro P, Ironside JW, Bell JE, Will RG. Creutzfeldt-Jakob disease in an individual occupationally exposed to BSE. Lancet 1993; 341: 642.

18. Will RG. Prions in animals. Virus and Life 1992; 4: 6--8.

19. Will RG, Ironside JW, Bell JE. Bovine spongiform Encephalopathy and risk to health. BMJ 1992; 305: 53.

20. Department of Health National Surveillance of Creutzfeldt-Jakob Disease. Bell JE and Ironside JW. Bulletin of the Royal College of Pathologists, April 1991, pp 9-10.

21. Bell JE, Ironside JW, McCardle L & Will RG. Creutzfeldt-Jakob disease - UK Neuropathology Project. Neuropathology and Applied Neurobiology 1992; 18: 302.

22. Ironside JW, Bell JE, McCardle L & Will RG. Neuronal and glial reactions in Creutzfeldt-Jakob Disease. Neuropathology and Applied Neurobiology 1992; 18: 295.

23. Ironside JW, McCardle L, Hayward P & Bell JE. Ubiquitin immunocytochemistry in human spongiform encephalopathies. Neuropathology and Applied Neurobiology 1993; 19: 134-140.

24. Prion Protein: Distribution and Significance in Creutzfeldt Jakob disease - Thesis submission by Philip Hayward for Degree of Honours BSc (Medical Science) in Department of Pathology.

25. Bell JE, Ironside JW. How to tackle a possible CJD necropsy. J Clin Path 1993; 46: 193-197.

26. Ironside JW, Bell JE, Hayward P. Glial and neuronal reactions in Creutzfeldt-Jakob disease. Clinical Neuropathology 1992; ii: pp226.

27. Ironside JW, Barrie C, McCardle L & Bell JE. Microglial cell reactions in human spongiform encephalopathies. Neuropathology & Applied Neurobiology 1993; 19(2): 57.

28. The Morphology, Distribution and Cellular Reactions to Amyloid Plaques in Neurodegenerative Diseases and the Aged Brain. Thesis submission to Edinburgh University by Christopher Turner for the degree of BSc (Hons) (Med Sci) in the Department of Pathology, Session 1992-1993.

29. Bell JE, Ironside JWI. Neuropathology of spongiform encephalopathies in humans. B. Med. Bull. 1993; 49: 738-777.

30. Will RG. Abstract: Prion Diseases in Man. 8th Wye College Neuropathology Symposium, 5-9 July 1993.

31. Prion Protein Pathology in Sporadic Creutzfeldt-Jakob Disease. Thesis submission to Edinburgh University by Simon Thomas MacDonald for the degree of BSc (Hons) (Med Sci) in the Department of Pathology 1994.

32. Tobias E, Mann C, Bone I, de Silva R, Ironside JW. A case of Creutzfeldt-Jakob disease presenting with cortical deafness (Letter). JNNP 1994; 57(7): 872-873.

33. Sutherland K, Ironside JW. Novel application of image analysis to the detection of spongiform change. Analytical and Quantitative Cytology and Histology 1994; 16(6): 430-434.

34. Sutherland K, Barrie C and Ironside JW. Automatic quantification of amyloid plaque formation in human spongiform encephalopathy. Neurodegeneration 1994; 3: 293-300.

35. de Silva R, Ironside JW, McCardle L, Esmonde T, Bell J, Will R, Windl O, Dempster M, Esitbeiro P, Lathe R. Neuropathological phenotype and "prion protein" genotype correlation in sporadic Creutzfeldt-Jakob disease. Neuroscience Letters 1994; 179: 50-52.

36. Alperovitch A, Brown P, Weber T, Pocchiari M, Hofman A and Will R. Incidence of Creutzfeldt-Jakob disease in Europe in 1993 (Letter). Lancet 1994; 343: 918.

37. de Silva R, Esmonde TFG. Iatrogenic transmission of Creutzfeldt-Jakob disease: an update. CNS Drugs 1994; 2(2): 96-101.

38. Will RG and Wilesmith JW. Response to the article: "Vertical transfer of prion disease" by Lacey and Dealler. Human Reproduction 1994; 9(10): 1792-1800.

39. Will RG. Epidemiology of Creutzfeldt-Jakob disease. British Medical Bulletin 1993; 49: 960-971.

40. Gray F, Chretien F, Cesaro P, Chatelain J, Beaudry P, Laplanche JL, Mikol J, Bell J, Gambetti Degos. Creutzfeldt-Jakob disease and cerebral amyloid angiopathy. Acta Neuropathol 1994; 88: 106-111.

41. Brown P, Cervenakova L, Goldfarb L, McCombie WR, Rubenstein R, Will RG et al. Iatrogenic Creutzfeldt-Jakob disease: an example of the interplay between ancient genes and modern medicine. Neurology 1994; 44: 291-293.

42. Brown P, Kenney K, Little B, Ironside JW, Safar J, Rohwer R, Roos R, Wollmann R, Gibbs CJ Jr, Gajdusek DC. Comparison of clinical features, neuropathology and intracerebral distribution of PrP amyloid protein in the brains of patients with spongiform encephalopathy. Neurobiol Aging 1994; 15 (Suppl 1): S150.

43. de Silva R, Ironside JW, Barrie C, Esmonde TFG, Bell JE, Will RG. Amyloid plaques in Creutzfeldt-Jakob disesae: prevalence and clinical correlates. Ann Neurol 1994; 36(2): 273.

44. de Silva R, Windl O, Dempster M, Estibeiro P, Esmonde TFG, Lathe R, Ironside JW, Will RG. Prion protein genotype in Creutzfeldt-Jakob disease: the Edinburgh experience. Ann Neurol 1994; 36(2): 272.

45. Will RG. Possible Creutzfeldt-Jakob disease in an adolescent. World Health Organisation Weekly Epidemiological Record 1995; 15: 105-106.

46. Esmonde TFG, Will RG, Ironside J, Cousens S. Creutzfeldt-Jakob disease: a case-control study. Neurology 1994; 44 (Suppl 2): A193.

47. Will RG. The United Kingdom and European CJD Surveillance System. Highlights and Developments. Abstract presented at OIE meeting in Paris 1-2 September 1994.

48. Will RG. The surveillance of Creutzfeldt-Jakob disease in the United Kingdom. In: Transmissible Spongiform Encephalopathies. Proceedings of a Consultation on BSE with the Scientific Veterinary Committee of the European Communities held in Brussels 14-15 September 1993. Eds: Bradley R & Marchant B. pp 143.

49. Will RG. Commentary: Gene influences of Creutzfeldt-Jakob disease. Lancet 1994; 344: 1310-1311.

50. Wientjens DPWM, Will RG, Hofman A. Creutzfeldt-Jakob disease: a collaborative study in Europe. JNNP 1994; 57: 1285-1299.

51. Hayward PAR, Bell JE, Ironside JW. Prion protein immunocytochemistry: reliable protocols for the investigation of Creutzfeldt-Jakob disease. Neuropathology and Applied Neurobiology 1994; 20: 375-383.

52. Sutherland K, Rutovitz D, Bell JE, Ironside JW. Evaluation of a novel application of image analysis to spogiform change detection. Proceedings of the IEEE International Conference in Imaging Processing, Austin TX, November 1994, pp 378-381.

53. Sutherland K, Barrie C, Ironside JW. Automatic image analysis of PrP plaque formation in human spongiform encephalopathy. Neuropathology and Applied Neurobiology 1994; 20: 518.

54. Will RG. Creutzfeldt-Jakob disease. Postgraduate Doctor Caribbean 1995; 11: 50-56.

55. Will RG. Creutzfeldt-Jakob disease. Postgraduate Doctor Middle East 1995; 18: 177-182.

56. Nicholl D, Windl O, de Silva R, Sawcer S, Dempster M, Ironside JW, Estibeiro JP, Yuill GM, Lathe R, Will RG. Inherited Creutzfeldt-Jakob disease in a British family associated with a novel 144 base pair insertion of the prion protein gene. JNNP 1995; 58: 65-69.

57. Goodbrand IA, Ironside JW, Nicolson D, Bell JE. Prion protein accumulation in the spinal cords of patients with sporadic and growth hormone associated Creutzfeldt-Jakob disease. Neuroscience Letters 1995; 183: 127-130.

58. Pickering-Brown SM, Mann DMA, Owen F, Ironside JW, de Silva R, Roberts DA, Balderson, Cooper PN. Allelic variations in apolipoprotein E and prion protein genotype related to plaque formation and age of onset in sporadic Creutzfeldt-Jakob disease. Neuroscience Letters 1995; 187: 127-129.

59. Sutherland K, Macdonald ST, Barrie C, Ironside JW. Assessment of neuropathological targeting in Creutzfeldt-Jakob disease: a quantitative immunocytochemical study. Neuropathology and Applied Neurobiology 1995; 15.

60. Jeffrey M, Goodbrand IA, Goodsir CM. Pathology of the transmissible spongiform encephalopathies with special emphasis on ultrastructure. Micron 1995; 26(3): 277-298.

61. Brown P, Kenney K, Little B, Ironside J, Will R, Cervenakova L, Bjork RJ, San Martin RA, Safar J, Roos R, Haltia M, Gibbs CJ Jr, Gajdusek DC. Intracerebral distribution of infectious amyloid protein in spongiform encephalopathy. Ann Neurol 1995; 38: 245-253.

62. Revesz T, Daniel SE, Lees AJ, Will RG. A case of progressive subcortical gliosis associated with deposition of abnormal prion protein (PrP). JNNP 1995; 58: 759-760.

63. Sutherland K, Goodbrand IA, Bell JE, Ironside JW. Objective quantification of prion protein in spinal cords of cases of Creutzfeldt-Jakob disease. Analytical Cellular Pathology (in press).

64. Sutherland K, Macdonald S, Ironside JW. Quantification and analysis of the neuropathological features of Creutzfeldt-Jakob disease. Journal of Neuroscience Methods (in press).

65. Goodbrand IA, Nicolson D, Bell JE, Ironside JW. Prion protein localization in the spinal cord and brain stem in iatrogenic and sporadic CJD: an immunocytochemical study with pathogenetic implications. Neuropathology and Applied Neurobiology (in press).

SECTION 6 STAFF

CLINICAL

Dr R.G. Will
Dr T.F.G. Esmonde (1990-1992)
Dr R. de Silva (1992-1994)
Dr M. Zeidler (1994 -)
Miss J. Mackenzie

NEUROPATHOLOGY LABORATORY

Dr J.W. Ironside
Dr J.E. Bell
Mrs L. McCardle
Miss C. Barrie
Ms A. Honeyman
Ms A. Mackenzie

RESEARCH STAFF FUNDED BY OTHER SOURCES

Dr K. Sutherland (BBSRC)
Dr I. Goodbrand (MRC)
Mr D. Nicolson (MRC)

MOLECULAR BIOLOGY

Dr J. Collinge, Prion Disease Group, St. Mary's Hospital, London.
Mr P. Estibeiro, Centre for Genome Research, University of Edinburgh.

STATISTICAL ANALYSIS

Professor P. Smith, London School of Hygiene and Tropical Medicine.
Mr S. Cousens, London School of Hygiene and Tropical Medicine.